REMARKS

Examiner Interview

Applicant would like to thank the Examiner for his helpfulness and courtesy during an interview held on Wednesday June 20, 2007. Examiner and Applicants' Representative discussed the pending rejections, Applicants' claims amendments and Applicants' arguments. Examiner and Applicants' Representative were in general agreement that the amendments and arguments proposed by the Applicant would result in allowable claims pending review by the Primary Examiner.

Rejection Under 35 USC § 112, second paragraph

Examiner has maintained the rejection of Claim 86. Examiner notes that the brackets around the letters "s" in the words "epitope[s]" and "group[s]" render the terms indefinite. Applicants intended to delete the letter "s" from the ends of the terms using double brackets as is permissible under MPEP 714, II, C, (B). Claims now have the permissible markings to denote deletion of the letters. Applicants respectfully request that the rejection be withdrawn.

The Examiner has rejected Claim 86 as being indefinite for the reasons given in the pending office action. Applicants respectfully disagree that the claim as written is indefinite. However and solely to advance their business interests, Applicants have amended Claim 86. Applicants respectfully request that the rejection be withdrawn.

Rejection Under 35 USC § 102(b)

Claim 86 is rejected under 35 USC § 102(b) as being anticipated by Vannier, *et al.* Vannier teaches an ELISA method for identifying antibodies from experimental samples using an ubiquitin-hFSHR fusion protein. In the Response to the previous Office Action (mailed 7/11/2006) Applicants amended Claim 86 by adding two limitations. 1) "A ubiquitin fusion protein comprising two or more identical epitopes." Examiner agrees with Applicants that the fusion protein of the cited prior art reference is unlikely to have two or more identical epitopes. 2) Three fusion sites wherein one of the sites is at the C-terminus of the ubiquitin protein and the site is non-cleavable. Examiner states "Vannier is silent as to whether or not the fusion site of the ubiquitin-FSHR fusion protein is cleavable and Applicants have presented no evidence supporting the assertion that it is cleavable." Here Applicants present the requested evidence.

It is known in the art that ubiquitin is a small eukaryotic protein. Ubiquitin is encoded by a family of genes whose translation products are fusion proteins. The expression of heterologous proteins as fusions to ubiquitin in either prokaryotic or eukaryotic host dramatically increase yield and allows the exposure of any amino acid following cleavage. However, the single exception is that ubiquitin is resistant to cleavage from the fusion protein when proline is the amino acid immediately following ubiquitin. The ubiquitin-proline bond is resistant to cleavage by ubiquitin-specific proteases. *See*, Baker, "Protein Expression Using Ubiqutin Fusion and Cleavage," Curr. Opin. Biotech., 1996 7:541-546, pp. 543, last paragraph. Ubiquitin-proline fusions do not occur naturally. The non-cleavable fusion proteins of the present invention have a non-native ubiquitin C-terminal sequence (*e.g.*, RGV; proline-glycine-valine) comprising a proline residue at the fusion junction to render it non-cleavable. *See*, pending specification, paragraph [0127].

Vannier has constructed ubiquitin fusion proteins to human FSHR (amino acids 23-358, 23-171 or 172-358; amino acid 23 is cysteine and amino acid 172 is leucine) and human LHR (amino acids 21-229 and 21-317; amino acid 21 is leucine). None of these protein sequences have proline at the end of the sequence (the N-terminus) that was fused with the C-terminus of the ubiquitin protein. Therefore, none of the fusion proteins made by Vannier were non-cleavable. Thus, Vannier can not anticipate the element of the claim wherein *the fusion site at the C-terminus of the ubiquitin protein ... is non-cleavable*.

Applicants believe that their arguments successfully overcome the Examiners' rejection and respectfully request that the pending rejection be withdrawn and the claims passed to allowance.

Rejection Under 35 USC § 102(b)

Claim 86 is rejected under 35 USC § 102(b) as being anticipated by Loosfelt, *et al.* Loosfelt teaches an ELISA method for identifying antibodies from experimental samples using an ubiquitin-hFSHR fusion protein. In the Response to the previous Office Action (mailed 7/11/2006) Applicants amended Claim 86 by adding two limitations. 1) "A ubiquitin fusion protein comprising two or more identical epitopes." Examiner agrees with Applicants that the fusion protein of the cited prior art reference is unlikely to have two or more identical epitopes. 2) Three fusion sites wherein one of the sites is at the C-terminus of the ubiquitin protein and

the site is non-cleavable. Examiner states "Loosfelt is silent as to whether or not the fusion site of the ubiquitin-FSHR fusion protein is cleavable and Applicants have presented no evidence supporting the assertion that it is cleavable." Here Applicants present the requested evidence.

It is known in the art that ubiquitin is a small eukaryotic protein. Ubiquitin is encoded by a family of genes whose translation products are fusion proteins. The expression of heterologous proteins as fusions to ubiquitin in either prokaryotic or eukaryotic host dramatically increase yield and allows the exposure of any amino acid following cleavage. However, the single exception is that ubiquitin is resistant to cleavage from the fusion protein when proline is the amino acid immediately following ubiquitin. The ubiquitin-proline bond is resistant to cleavage by ubiquitin-specific proteases. *See*, Baker, "Protein Expression Using Ubiqutin Fusion and Cleavage," Curr. Opin. Biotech., 1996 7:541-546, pp. 543, last paragraph. Ubiquitin-proline fusions do not occur naturally. The non-cleavable fusion proteins of the present invention have a non-native ubiquitin C-terminal sequence (*e.g.*, RGV; proline-glycine-valine) comprising a proline residue at the fusion junction to render it non-cleavable. *See*, pending specification, paragraph [0127].

Loosfelt has constructed ubiquitin fusion proteins to human TSHR (amino acids 19-243 or 604-764; amino acid 19 is leucine and amino acid 604 is isoleucine). Neither of these protein sequences have proline at the end of the sequence (the N-terminus) that was fused with the C-terminus of the ubiquitin protein. Therefore, none of the fusion proteins made by Loosfelt were non-cleavable. Thus, Loosfelt, can not anticipate the element of the claim wherein *the fusion site at the C-terminus of the ubiquitin protein ... is non-cleavable.*

Applicants believe that their arguments successfully overcome the Examiners' rejection and respectfully request that the pending rejection be withdrawn and the claims passed to allowance.

Rejection Under 35 USC § 103

Claim 86 is rejected under 35 USC § 102(b) as being obvious in view of Vannier, *et al.*, in further view of Loosfelt, *et al.* Examiner states that neither Loosfelt or Vannier teach the ubiquitin fusion proteins of part (a)i) and (a)ii). In view of the arguments made above, Applicants submit that Loosfelt and Vannier do not teach the ubiquitin fusion proteins of part (a)iii) or (a)iv) for the reasons presented above. A finding of obviousness requires the teaching

of each element of the claimed invention in the prior art. MPEP 2143. Vannier and Loosfelt do not teach all of the elements of the present invention alone or in combination. As can be seen from the limitations of the pending claim, the fusion proteins of the instant invention are not typical of the types used in the art at the time of the invention. Applicants submit that it was unknown in the art at the time of the invention and filing of the application that the fusion proteins of the present invention would be effective in the detection of antibodies since the fusion proteins of the instant invention are made at ubiquitin sites (*e.g.*, at the N-terminus or internally) not typically used and/or with proteins not found natively (*e.g.*, with multiple identical epitopes or with non-cleavable epitopes).

Applicants believe that their arguments successfully overcome the Examiners' rejection and respectfully request that the pending rejection be withdrawn and the claims passed to allowance.

Summary

In light of the above amendment, consideration of the subject patent application is respectfully requested. Any deficiency or overpayment should be charged or credited to Deposit Account No. 500282.

Respectfully submitted,

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